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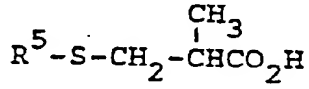
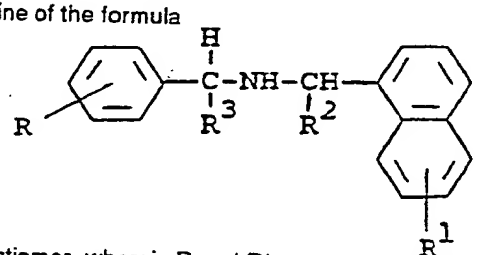
(54) Optical resolution of DL-3-acylthio-2-methylpropanoic acid using an optically active amine

(57) A process for the optical resolution of DL-3-acylthio-2-methylpropanoic acid comprises contacting DL-3-acylthio-2-methylpropanoic acid of the structure



wherein R^5 is acetyl with an optically active amine of the formula



which is the R-(+) enantiomer or the S-(-) enantiomer, wherein R and R^1 are independaently selected from H, C_{1-12} alkyl or halogen, R^2 is H or C_{1-12} alkyl and R^3 is C_{1-12}alkyl, to form diastereoisomeric salts, subjecting the so-formed diastereoisomeric salts to fractional crystallization in a solvent to separate the D-acid salt from the L-acid salt, and then treating the individual diastereoismeric salt with acid to form D-(-)-3-acylthio-2-methyl-propanoic acid and L-(-)-3-acylthio-2-methyl-propanoic acid and L-(-)-3-acylthio-2-methylpropanoic acid. A method for preparing the optically active amine is also provided.

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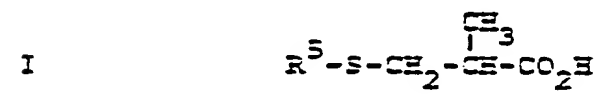
OPTICAL RESOLUTION OF DL-3-ACYLTHIO-2-METHYLPROPANOIC ACID USING AN OPTICALLY ACTIVE AMINE

The present invention relates to a method for resolving DL-3-acylthio-2-methylpropanoic acid employing an optically active amine and to a method for preparing the optically active amine.

In accordance with the present invention, a process is provided for the optical resolution of DL-3-acylthio-2-methylpropanoic acids which includes the steps of contacting a DL-3- acetylthio-2-methylpropanoic acid of the structure I

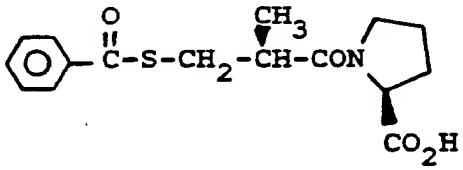
I 

wherein R^5 is acetyl with an optically active amine of formula II. The reaction is carried out in the presence of an organic solvent such as isopropyl alcohol, sec-butanol or isobutyl acetate employing a molar ratio of acid I to amine II of within the range of from about 1.05:1 to about 1:1, while heating the reaction mixture to a temperature within the range of from about 15°C to

about 40°C, to form diastereoisomeric salts, subjecting the so-formed diastereoisomeric salts to fractional crystallization to separate the D-acid salt from the L-acid salt, and then treating the individual diastereoisomeric salt with acid, such as hydrochloric acid, sulphuric acid or perchloric acid employing a molar ratio of salt to acid of within the range of from about 0.5:1 to about 2.0:1, to form D-(-)-3-acylthio-2-methylpropanoic acid and L-(-)-3-acylthio-2-methylpropanoic acid.

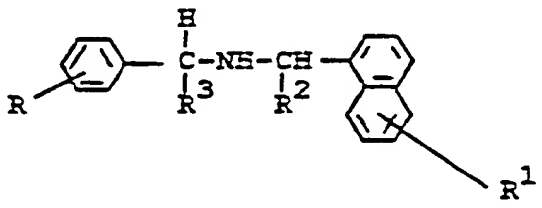
The individual diastereomeric salt may also be converted to the free acid by first partitioning between an organic solvent such as dichloromethane or toluene and an aqueous base such as aqueous sodium hydroxide or sodium carbonate, separating the aqueous layer, acidifying with aqueous acid and extracting the recovered acid into an organic solvent such as dichloromethane or toluene.

The recovered D-(-)-3-acylthio-2-methyl-propanoic acid may then be employed as a starting material to prepare captopril (formula IV where R^5 is acetyl) or



which also has antihypertensive properties.

The optically active amine which is useful in optically resolving DL-3-acetylthio-2-methylpropanoic acid has the structure

II. 

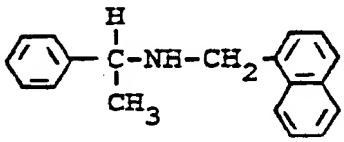
and includes the R-(+) enantiomer and the S-(-)enantiomer, wherein R and R^1 may be the same or different but are independently selected from H, lower alkyl or halogen, R^2 is H or lower alkyl, and R^3 is lower alkyl.

The term "lower alkyl" or "alkyl" as used herein refers to straight and branched chain radicals of up to 12 carbons and preferably 1 to 8 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, including the various branched chain isomers thereof.

The term "halogen" or "halo" as used herein refers to chlorine, bromine, fluorine or iodine with chlorine being preferred.

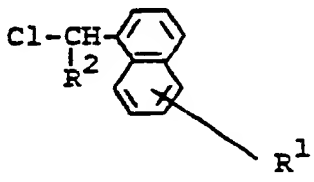
Preferred optically active amines of formula I are the R-(+) enantiomer where R, R^1 and R^2 are each H. Most preferred is the R-(+) enantiomer of the compound IIA

IIA



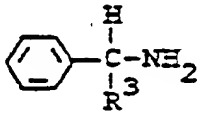
The optically active amines of formula II is prepared by forming a solution of a compound of the structure

III



in an organic solvent such as toluene, ethyl acetate, chloroform or methylisobutyl ketone and an organic base such as triethylamine, tripropyl

amine or tributylamine, treating the solution with an amine of the structure

IV 

employing a molar ratio of III:IV of within the range of from about 1.05:1 to about 1.2:1, heating the mixture to a temperature within the range of from about 70 to about 120°C, under an inert atmosphere, such as nitrogen, to form the compound of formula II and recovering such compound from the reaction mixture.

The following Examples represent preferred embodiments of the invention. Unless otherwise indicated, all temperatures are expressed in degrees Centigrade.

Example 1

Preparation of R-(+)-N-(1-Naphthylmethyl)-α-methylbenzylamine [R(+)-amine]

1-Chloromethylnaphthalene (154 g, 1.05 equivalents) was dissolved in toluene (400 ml) with triethylamine (130 ml) and purged with nitrogen for 10 minutes.

R-(+)-α-methylbenzylamine (100 g) was added and the solution heated at 70-75°C under nitrogen for 20 hours during which time a precipitate of triethylamine hydrochloride formed. The mixture was cooled to ambient and washed with water (200 ml) to remove triethylamine hydrochloride. The toluene was evaporated, the residue dissolved in methylene chloride (600 ml) and water (200 ml) added. Concentrated hydrochloric acid (150 ml) was added over 20 minutes to form amine hydrochloride precipitate. The precipitate was filtered and washed with water (400 ml). The solid was slurried in methylene chloride (500 ml), filtered and washed with methylene chloride (100 ml). The amine was isolated by basifying the salt to pH 13.0, separating the methylene chloride layer, drying over sodium sulphate and evaporating to dryness. Weight of amine was 122 g, 56.5%. $\alpha_D^{ethanol} = +34°$.

The structure was confirmed by ^1H and ^{13}C NMR and microanalysis of the hydrochloride salt. C_{19}

H_{20} N Cl found (theory): C, 76.90 (76.63); H, 7.00 (6.72); N, 4.62 (4.70); Cl, 11.83 (11.93) %.

Example 2

Resolution of DL-3-Acetylthio-2-methylpropanoic Acid with R-(+)-N-(1-Naphthylmethyl)-α-methyl Benzylamine

DL-3-Acetylthio-2-methylpropanoic acid (32.56 g, 0.20 mole) and R-(+)-N-(1-naphthylmethyl)-α-methylbenzylamine (50 g, 0.19 mole, 0.95 equivalent) were dissolved in isopropyl alcohol (270 ml) by warming to about 40°C. A clear solution was obtained which was cooled to 30°C, seeded and the temperature allowed to drift to ambient (18°C). During 2 hours a crop of fluffy crystals formed. The mixture was left overnight in a refrigerator at 0-2°C, without agitation. The crystals were filtered and washed with cold (0-2°C) isopropyl alcohol (25 ml), and dried at 55°C under vacuum to yield 27.6 g of crude salt.

The salt was recrystallized from isopropanol (110 ml) by warming to 45°C, cooling to 30°C, seeding and allowing the solution to drift to ambient temperature without stirring. A thick precipitate formed within 2 hours. The mixture was cooled in the refrigerator overnight, filtered, washed with cold isopropyl alcohol (20 ml), and dried under vacuum at 55°C to yield 24 g of salt.

The salt was dissolved in methylene chloride (100 ml) and water (150 ml) added. The pH was adjusted to 10.5 by addition of 10 M NaOH with vigorous agitation. The layers were

separated, and the aqueous layer was washed with methylene chloride (40 ml x 2). The methylene chloride layer was retained for amine recovery.

Fresh methylene chloride (80 ml) was added to the aqueous phase which was then acidified to pH = 1.5 with hydrochloric acid. The layers were separated and the aqueous layer washed with methylene chloride (40 ml x 2). The combined methylene chloride was dried over sodium sulphate, filtered and evaporated to leave an oil.

Yield of (-) acid = 9.1 g; $\alpha_D^{\text{ethanol}} = -44.5°$.

Optical purity 96.6%.

The amine was recovered as follows:

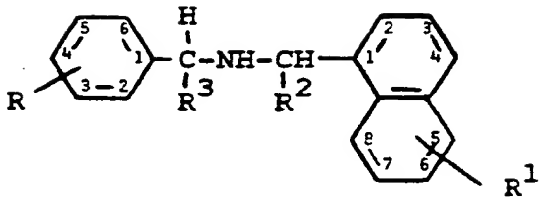
a) The methylene chloride phase above was concentrated to yield 15.1 g of amine.

b) The combined isopropyl alcohol mother liquors were concentrated to an oil which was dissolved in methylene chloride (120 ml). Water (150 ml) was added and the pH adjusted to 10.5 by addition of 10 M NaOH. The layers were separated and the aqueous layer washed with methylene chloride (40 ml x 2). The combined methylene chloride was dried and evaporated to yield 31.5 g of amine.

Total recovery of amine was 46.6 g, 93%.

Examples 3 to 15

Following the procedure of Example 1, using appropriate reagents, the following additional optically active organic amines may be prepared.



Ex. No.	R(position)	R^3	R^2	R^1(position)
3.	CH_3(4)	CH_3	H	H
4.	Cl(4)	C_2H_5	CH_3	CH_3(6)
5.	H	C_3H_7	H	C_2H_5(5)
6.	C_2H_5(3)	C_4H_9	C_2H_5	H
7.	Br(3)	CH_3	H	CH_3(5)
8.	H	C_2H_5	C_3H_7	CH_3(7)
9.	C_3H_7(4)	C_3H_7	H	H
10.	H	C_4H_9	C_4H_9	H
11.	H	CH_3	H	CH_3(6)
12.	Cl(3)	C_2H_5	C_5H_{11}	CH_3(5)
13.	CH_3(4)	C_3H_7	CH_3	CH_3(7)
14.	H	C_4H_9	H	H
15.	H	CH_3	H	CH_3(6)

Example 16

S-(-)-N-(1-Naphthylmethyl)-α-methylbenzylamine

Following the procedure of Example 1 except substituting S-(-)-α-methylbenzylamine for R-(+)-α-methylbenzylamine, the title compound is obtained.

Example 17

Resolution of DL-3-Benzoylthio-2-methylpropanoic Acid with R-(+)-N-(1-naphthylmethyl)-α-methylbenzylamine

Following the procedure of Example 2 except substituting DL-3-benzoylthio-2-methylpropanoic acid for DL-3-acetylthio-2-methylpropanoic acid, resolution is accomplished.

Example 18

Resolution of DL-3-Benzoylthio-2-methylpropanoic Acid with S-(-)-N-(1-naphthylmethyl)-α-methylbenzylamine

Following the procedure of Example 2, except substituting S-(-)-N-(1-naphthylmethyl)-α-methylbenzylamine for R-(+)-N-(1-naphthylmethyl)-α-methylbenzylamine, the above benzoyl compound is resolved.

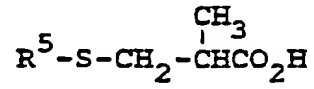
Example 19

Resolution of DL-3-Acetylthio-2-methylpropanoic acid with S-(-)-N-(1-naphthylmethyl)-α-methylbenzylamine

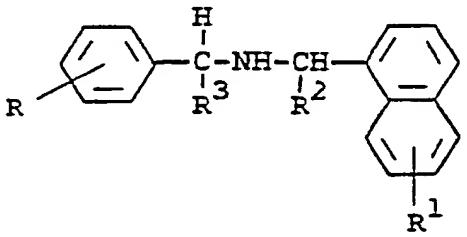
Following the procedure of Example 2 except substituting S-(-)-N-(1-naphthylmethyl)-α-methylbenzylamine for R-(+)-N-(1-naphthylmethyl)-α-methylbenzylamine, the resolution is accomplished.

CLAIMS

1. A process for the optical resolution of DL-3-acylthio-2-methylpropanoic acid, which comprises contacting DL-3-acylthio-2-methylpropanoic acid of the structure



wherein R^5 is acetyl with an optically active amine of the formula



which is the R-(+) enantiomer or the S-(-) enantiomer, wherein R and R^1 are independently selected from H, lower alkyl or halogen, R^2 is H or lower alkyl and R^3 is lower alkyl, to form diastereoisomeric salts, subjecting the so-formed diastereoisomeric salts to fractional crystallization in a solvent to separate the D-acid salt from the L-acid salt, and then treating the individual diastereoisomeric salt with acid to form D-(-)-3-acylthio-2-methylpropanoic acid and L-(-)-3-acylthio-2-methylpropanoic acid.

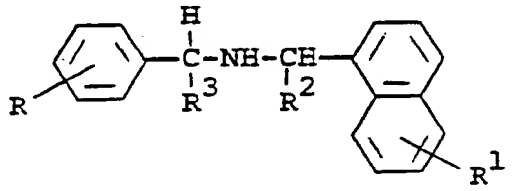
2. The process as defined in Claim 1 wherein R, R^1 and R^2 are each H and R^3 is CH_3.

3. The process as defined in Claim 1 wherein the DL-3-acylthio-2-methylpropanoic acid is DL-3-acetylthio-2-methylpropanoic acid.

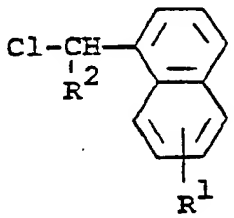
4. The process as defined in Claim 1 wherein the R-(+) enantiomer of the optically active amine is employed.

5. The method as defined in Claim 1 wherein the optically active amine has the name R-(+)-N-(1-naphthylmethyl)-α-methylbenzylamine.

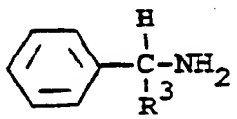
6. A method for preparing an optically active amine compound of the formula



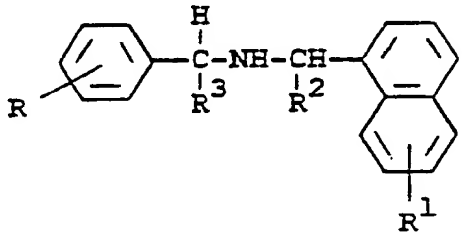
wherein R and R^1 are independently H, lower alkyl or halogen, R^2 is H or lower alkyl, and R^3 is lower alkyl, including the R-(+)-enantiomer or the S-(-)-enantiomer, which comprises treating a solution of a compound of the structure



and an organic base with an amine of the structure



heating the reaction mixture to a temperature within the range of from about 70 to about 120°C and recovering the compound of the structure



7. The method as defined in Claim 6 wherein said organic base is triethylamine.

8. The method as defined in Claim 6 wherein R, R^1 and R^2 are each H and R^3 is CH_3.

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